



CNS module

Pharmacology

Anti-epileptic drugs



Learning Outcomes (LOs)

1. Identify different group of drugs used in treatment of epilepsy.
2. Describe the mechanism of action of antiepileptic drugs.
3. Compare between different mechanism of action of antiepileptic drugs .
4. Describe the drug interaction of antiepileptic drugs.
5. List adverse effects of antiepileptic drugs.



DRUG THERAPY OF EPILEPSY

■ Definition of Epilepsy

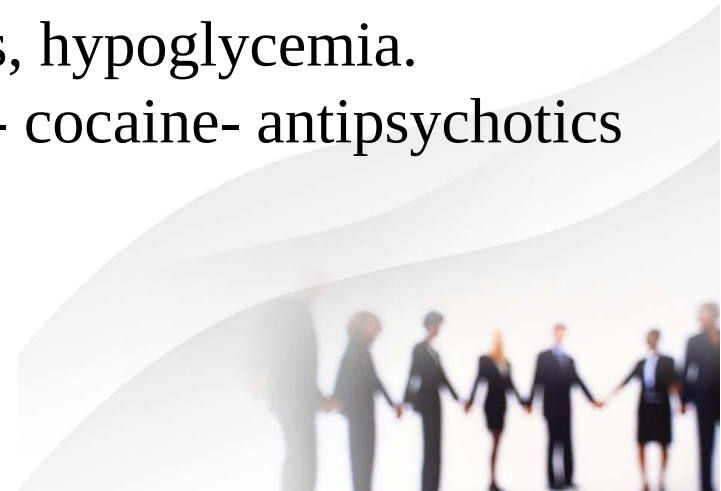
- Chronic disease characterized by repeated attacks (seizures or fits) of abnormal electrical discharge of cerebral neurons resulting in EEG, motor, sensory, autonomic or psychological changes.

■ Etiology

A. Primary epilepsy (unknown cause, i.e. idiopathic).

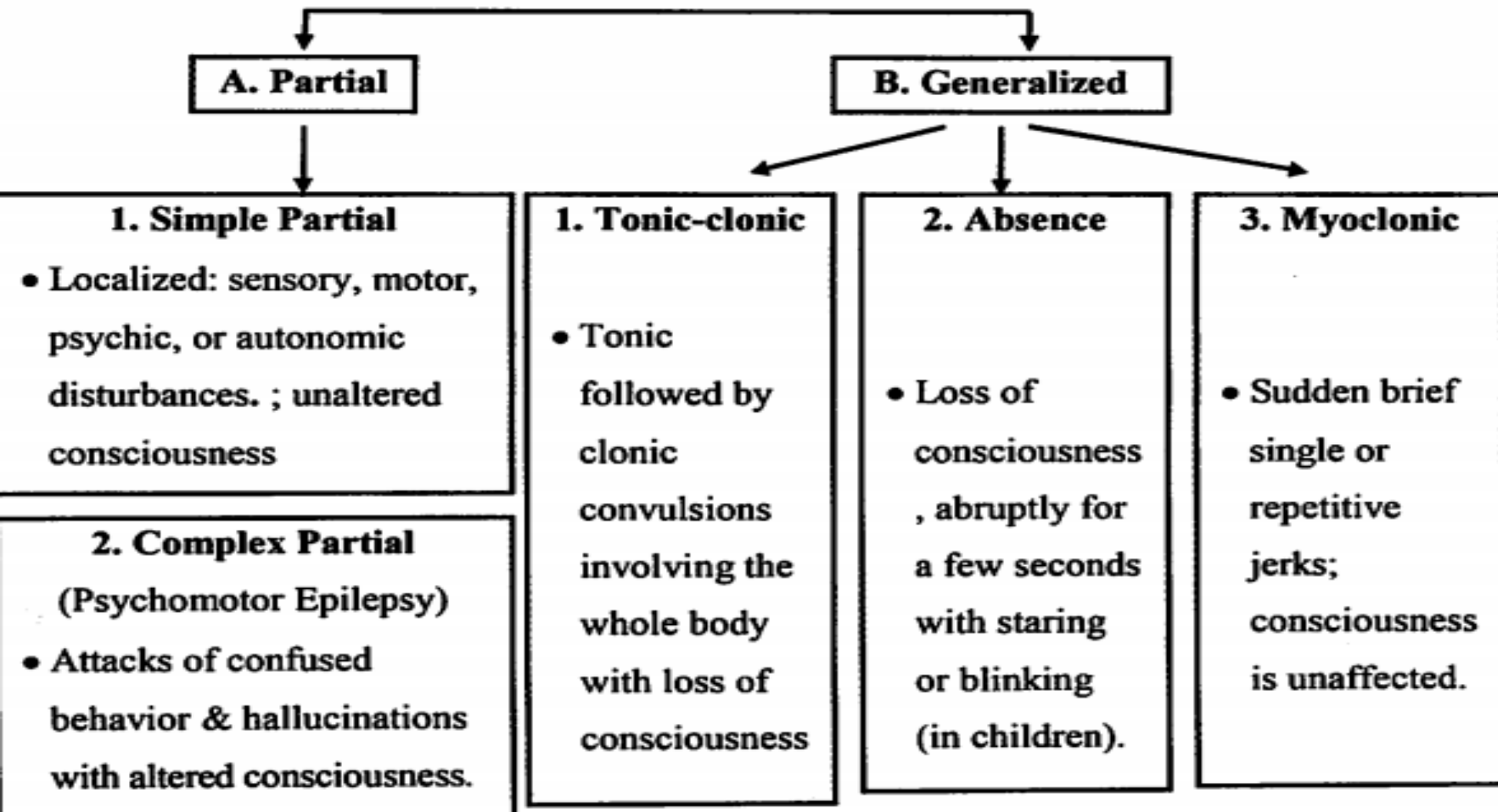
B. Secondary epilepsy caused by:

1. Trauma, meningitis, brain tumors, fevers, hypoglycemia.
2. Drugs: insulin (hypoglycemia) - TCAs - cocaine- antipsychotics - Li⁺.



■ Classification of Epilepsy

- Epilepsy is caused by a group of hyper excitable neurons with excessive electrical discharge which might be localized (partial) or spread (generalized)



Antiepileptic Drugs

■ Members

I. Classic agents (major or older agents) = First generation:

- **Phenytoin - carbamazepine - valproate.**
- **Phenobarbital - benzodiazepines.**

II. Newer agents = second generation:

- **Lamotrigine - levetiracetam - oxcarbazepine.**
- **Topiramate - gabapentin- pregabalin.**



■ Mechanism of Action

- Anti-epileptics block initiation or spread of seizures by hyper-excitability of cerebral neurons by acting on neurotransmitters or by blocking ion channels.

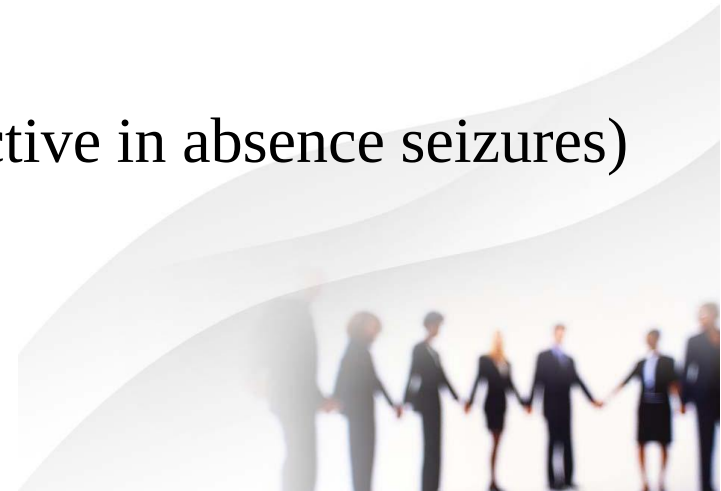
- **Most antiepileptic drugs act by more than one mechanism:**

1. Blockade of Na Channels

- Phenytoin- carbamazepine- valproate.
- Topiramate - lamotrigine.

2. Blockade of T- type Ca Channels (effective in absence seizures)

- Ethosuximide.
- Valproate.



3. Blockade of presynaptic voltage gated Ca Channels -> glutamate release.

- Lamotrigine.
- Gabapentin - pregabalin.

4. Binding to vesicle protein -> modify release of glutamate.

- Levetiracetam.

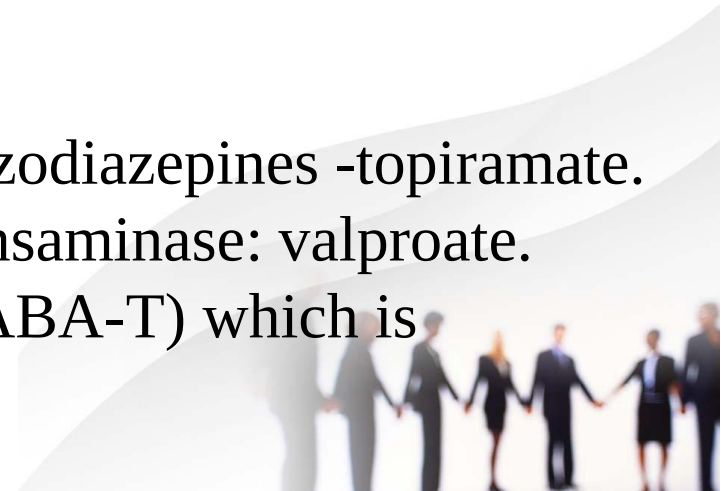
Newer agents: - lacosamide - zonisamide- rufinamide- felbamate, vigabatrin- tiagabine, preampcncl.

5. NMDA glutamate receptor antagonists:

- Valproate.

6. Effects on GABA

- Facilitate GABA action: phenobarbital -benzodiazepines -topiramate.
- $\wedge$ GABA Level : inhibits breakdown by transaminase: valproate.
-inhibits the enzyme GABA transaminase (GABA-T) which is responsible for inactivating GABA.



■ Therapeutic Uses

1. Epilepsy.

2. Mood stabilizers in bipolar depression:

- Lamotrigine - valproate - carbamazepine.

3. Neuropathic pain (trigeminal neuralgia, post herpetic & diabetic neuralgia):

- Carbamazepine- gabapentin - pregabalin.

4. Migraine:

- Valproate - topiramate.

5. Antiarrhythmic:

- Phenytoin.



■ Choice of Antiepileptic Drugs in Different Types of

Partial³³	Tonic- clonic³⁴	Absence³⁵	Myoclonic³⁶
<u>First line</u>			
• Carbamazepine • Lamotrigine.	• Valproate. • Lamotrigine.	• Ethosuximide. • Valproate	• Valproate.
<u>Alternatives</u>			
• Levetiracetam • Valproate • Oxcarbazepine	• Carbamazepine. • Oxcarbazepine	• Lamotrigine.	• Levetiracetam • Topiramate.

■ Adverse Effects & Precautions of Major (classic) Anti-epileptics

	Phenytoin	Carbamazepine	Valproate
Hypersensitivity	Skin rash → stop drug		
GIT Disturbances	Nausea - vomiting - epigastric pain (most common with valproic acid) → give small dose after meals.		
Neurological Disturbances (specially in toxic doses)	• Nystagmus, diplopia. • Ataxia. • Drowsiness. • ↓ Learning in children.	• Diplopia. • Ataxia. • Drowsiness.	• Fine hand tremors. • Ataxia. • Less sedative.
Effects on Hepatic Microsomal Enzymes (monotherapy is preferred)	Enzyme inducer • ↑ Metabolism of other antiepileptics. • Osteomalacia: ↑ vitD metabolism (→ vit D & Ca²⁺ supplements).	Enzyme inducer • ↑ Metabolism of antiepileptics, warfarin & other drugs.	Enzyme inhibitor • ↓ Metabolism of antiepileptics & other drugs.

Hematological Effects (→regular blood picture)	• Megaloblastic anemia 'supplement folic acid' • Lymphadenopathy	• Leukopenia • Agranulocytosis	• Thrombocytopenia
Teratogenicity → give folic acid	• Cleft palate & lip - heart anomalies.	• Less teratogenic .	• Spina bifida. • Neural tube defect.
Others	1. Cosmetic changes • Gingival hyperplasia (→gum hygiene). • Coarse facial features. • Hirsutism - acne. 2. Unpredictable serum level→ monitor serum level.	• Water intoxication & dilutional hyponatremia (potentiates ADH).	• <u>Hepatotoxicity</u> (rare but fatal). • Hair loss. • ↑ Appetite. • ↑ Body weight.

■ Specific adverse effects of newer antiepileptics:

- Newer agents are generally better tolerated with fewer drug interactions than the older agents.
- **Lamotrigine**: rash -• fatal dermatitis (Stevens-Johnson syndrome), hypersensitivity.
- **Topiramate**: renal stones- myopia (—• glaucoma)- weight loss- hypohydrosis.
- **Levetiracetam**: mood & behavioral changes.
- **Gabapentin /Pregabalin**: sedation, ataxia, weight gain- peripheral edema.
- **Vigabatrin**: Irreversible peripheral visual field defects



■ Drug interaction:

- **Phenobarbitone** produces competitive inhibition of metabolism of phenytoin then induction of microsomal enzymes, So, it initially enhances and later reduces the pharmacological activity of phenytoin. The net effect is unpredictable.
- **Phenytoin** is a potent hepatic enzyme inducer. it increase the degradation of other drugs e.g. digitoxin , warfarin , carbamazepine, oral contraceptives, folic acid , vit.D , vit.K and its own.
- **Carbamazepine** is a powerful enzyme inducer of hepatic microsomal enzymes.
So, enhances the metabolism of many other drugs e.g. phenytoin, oral contraceptives, warfarin and corticosteroids.



Valproate → **enzyme inhibitor** decrease phenytoin, carbamazepine, and barbiturate metabolism.

- It displaces phenytoin from plasma protein.

Plasma protein:

- **Some drugs displace it from pp**

 - salicylates, phenylbutazone, Sulphonamides and valproate displace the phenytoin from plasma protein and increase its free level.

- **Other drugs phenytoin displace it from pp**

 - thyroxine and TCA.

N.B: Fosphenytoin: used IV and more soluble and can taken IM



■ General guidelines for antiepileptic drug therapy

1. Proper diagnosis of type of epilepsy & prescribing the appropriate drug (wrong choice may worsen the condition).
2. Monotherapy is preferred since anti-epileptics are either enzyme inducers (phenytoin, carbamazepine & phenobarbital) or enzyme inhibitors (valproate).
3. Start therapy with a small dose & a single drug and gradually increase dose. If no effect is noted, gradually substitute or add another drug.
4. Long duration of treatment: If epileptic fits are absent for 2 years, consider terminating therapy; but if fits recur, repeat treatment for another 2 years.
5. Gradual drug withdrawal: over 6 months to avoid status epilepticus or relapse.



6. Folic acid supplements: especially in child bearing period to avoid teratogenic risk.

7. Pregnancy & child bearing period: Be aware of potential effect of valproate in pregnancy. Pregnant females should receive the lowest effective dose of the drug (do not stop drug as seizures may be harmful to fetus).

- Pregnancy increase metabolism of anti-epileptics -> adjust dose.
Anti-epileptics may reduce efficacy of contraceptives.

8. Periodic monitoring of serum level of drugs, since a drop below therapeutic level -> loss of seizure control while an increase in level - toxicity (CNS depression - coma - respiratory depression).

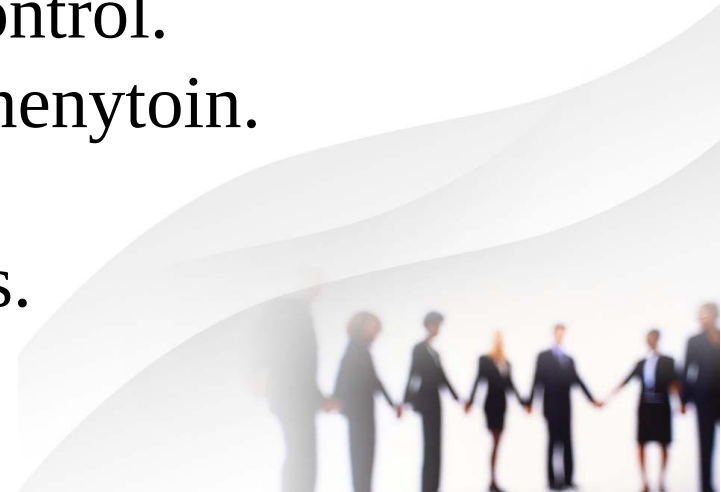
9. Sedation & tolerance limit the use of phenobarbital & clonazepam.



➤ **Management of Status Epilepticus:**

- Continuous or repetitive seizures with impaired consciousness in-between fits. (drugs are given **IV**).

1. **Lorazepam, midazolam or diazepam** (IV or rectal) —
for rapid control.
2. **Fosphenytoin or phenytoin** —> long-acting, to maintain control.
3. **Phenobarbital** —> 2nd choice to phenytoin.
4. **IV anesthesia** —> in resistant cases.



References

1. Lippincott illustrated Review of pharmacology: 18th ed.
2. Katzung, B.G. : Basic & clinical pharmacology, 14th ed.,
Mc Graw Hill Medical.

